REMARKS/ARGUMENTS

Claims 1-58 were pending. Claims 3, 4, 8-12, 19-43, 46-58 were withdrawn from further consideration as directed to non-elected subject matters in the present application before the amendment as set forth above. By this Amendment, claims 1, 16, and 44 are amended, new claims 59-60 are introduced, and claims 13-15 are withdrawn.

Claims 1, 16, and 44 have been amended to more clearly define the claimed invention. New claims 59-60 have been introduced to conform claims to the embodiments of the invention disclosed in the specification.

The support for the amendments can be found in the application as originally filed. For example, the support for the new claims can be found in the specification, Tables 1 and 2.

Applicants assert that no new matter is added.

Any amendments to the claims not specifically referred to herein as being included for the purpose of distinguishing the claims from cited references are included for the purpose of clarification, consistence and/or grammatical correction only.

Applicants appreciate the Examiner's careful review of the application.

Claim Set

In the Office Action dated August 24, 2006, the Examiner asserted that "the status of Claims 13-15 as 'original' is incorrect. The status of said claims is withdrawn."

Applicants respectfully traverse the Examiner's assertion for the reasons that had been set forth in the prior response to the February 21, 2006 Office Action under the heading "Restriction Requirements." To facilitate the prosecution, however, Applicants have withdrawn claims 13-15 from consideration for now as set forth in the above claim amendments.

Specification Objections

The Examiner also objected to the specification because the June 20, 2006 amendment stating "the disclosure of which is hereby incorporated herein in its entirety by reference introduced New Matter to the specification."

In response, Applicants have amended the specification to overcome the objection.

Drawings Objections

The Examiner objected to Figs. 1-4 for "being confusing. Neither said figures nor the legends thereto explain the labeling found in figures."

Applicants have amended the legends to Figs. 1-4 to clarify the labeling found in the figures. The support for the Amendment can be found in the specification, for examples, on page 13, lines 25-27. Accordingly, Applicants respectfully request that the objections to Figs. 1-4 be withdrawn.

Claim Objections

The Examiner objected to claim 44 "for being dependent from a non-elected claim."

Applicants have amended claim 44 to overcome the objection. Accordingly, Applicants respectfully request that the objection to claim 44 be withdrawn.

Claim Rejections Under Double Patenting

The Examiner maintained rejection of claims 1, 5-7, 16, 17, 44 and 45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5-7, 9, 10, 12 and 13 of the U.S. Patent 6,706,512. The Examiner also rejected claims 2 and 18 as being unpantable over claims 2 and 11, respectively, of the U.S. Patent 6,706,512 for the same reason.

In response, Applicants respectfully submit that a terminal disclaimer will be submitted after all other rejections with respect to these claims, in particular the rejections under 35 U.S.C. § 103, have been finally disposed of in a future Office Action.

Claim Rejections – 35 USC § 112 First Paragraph

Enablement and Written Description:

The Examiner maintained rejection of claims 1, 5-7 and 16 under 35 U.S.C. §112, first paragraph, for lack of enablement, and rejected claims 2 and 8 on the same ground. Specifically,

the Examiner asserted that "determining which of all polypeptides having at least 80% homology to SEQ ID NO: 3 have the desired activity would require undue experimentation."

The Examiner also maintained rejection of claims 1, 7, and 16 under 35 U.S.C. §112, first paragraph, for insufficient description, and rejected claims 2 and 8 on the same ground. Specifically, the Examiner asserted that "the polypeptides encompassed by the recited genus have any or no activity."

Applicants respectfully traverse both the enablement and insufficient description rejections for the reasons set forth in prior response. To facilitate the prosecution, however, Applicants have amended independent claims 1 and 16 such that amended claims 1 and 16 require the amino acid sequence "set forth in SEQ ID NO: 3," which makes the 35 U.S.C. §112, first paragraph rejections moot. The specification provides a reasonable amount of guidance to enable and sufficient description to support the variant having amino acid sequence "set forth in SEQ ID NO: 3."

Accordingly, Applicants respectfully request the 35 U.S.C. §112, first paragraph, rejection be withdrawn.

35 U.S.C. §103 Rejections

The Examiner maintained rejection of claims 1, 5-7, 16, 17, 44 and 45 under 35 U.S.C. §103(a) as being unpatentable over Gibbs et al., 1996 in view of Arosio et al., 2000 or Ayala et al., 2001. The Examiner also rejected claims 2 and 18 as being unpatentable under 35 U.S.C. §103(a) as being unpatentable over Gibbs et al., 1996 in view of Arosio et al., 2000 or Ayala et al., 2001 for the same reason.

In rebutting the Applicants' arguments for nonobviousness, the Examiner made the following allegations:

(A) Neither Gibbs et al. nor Arosio et al. are required to disclose a thrombin variant having both W215A and E217A, since this is a rejection under 35 U.S.C. 103(a).

(B) Arosio et al. "statement does not teach away from looking for additional single or multiple mutations that produce a thrombin variant that has even better anti-coagulant activity," or "teach away from making a double W215A+E217A mutant, or any other mutant," and "[m]oreover, Arosio et al. teach that further studies are necessary to identify more precisely the

epitopes for protein C binding and that the penultimate ß-strand of thrombin's B chain, which includes residues 215-217, represents an important target for future mutagenesis studies."

(C) The "synergistic effect is not unexpected" and that "many enzymes have allosteric sites that act synergistically in both the activation and inhibition of the enzyme." Citing Metzler et al (2001).

(D) "The skilled artisan would know that it is the ratio of protein C activity to fibrinogen clotting activity (PC/PF), not the absolute protein C activity, that determines whether the action of thrombin will be primarily anti-coagulation, via the activation of protein C, or procoagulation, via cleavage of thrombin (Arosio et al, pg 8095, parg1)."

Before replying to the Examiner's aforementioned points (A)-(D), Applicants want to direct the Examiner's attention to the MPEP rules on the 35 U.S.C. 103 as it will be the basis of the Applicants' response.

MPEP states that when applying 35 U.S.C. 103, "***the references*** must be considered as a whole and ***must suggest the desirability and thus the obviousness of making the combination***;" and "[t]he references must be viewed ***without the benefit of impermissible hindsight vision afforded by the claimed invention***." *See* §2141. (Emphasis added.)

MPEP further states that suggestion or motivation to modify the references must meet, among others, the following requirements:

I. ***The prior art must suggest the desirability of the claimed invention***;

II. The mere fact that references ***can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination***; and

III. A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" ***because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without*** some objective reason to combine the teachings of the references. *See* §2143.01. (Emphasis added.)

Applying the MPEP rules, Applicants hereby address each point raised by the Examiner in the Final Office Action regarding the motivation to combine and the unexpected properties of the claimed invention as follows:

(Reply A): The claimed invention is directed to a variant thrombin comprising an amino acid sequence having the substitutions W215A and E217A. The invention E217A/W215A possesses unexpected synergistic properties as shown in the attached Exhibit A. ***Neither the primary reference nor the secondary reference provides the motivation to combine the references to do what the invention has done.***

In the First Office Action dated February 21, 2006, the Examiner asserted that:

> "[i]t would have been obvious to a person of ordinary skill in the art to combine the teachings of Gibbs with Arosio to prepare a thrombin variant comprising both W215A and E217A substitutions. ***Suggestion to do so is provided by Arosio et al.***, wherein they state that W215 and E217 are known to be important for thrombin function. Furthermore, ***suggestion and motivation to combine is based on the skilled artisan's desire to provide a thrombin variant with enhanced protein C activation and decreased fibrinogen cleavage.***" (Emphasis added.)

See First Office Action, page 13.

In the Final Office Action dated August 24, 2006, the Examiner shifted the basis of motivation after Applicants had responded by pointing out that the ***combination of E217A and W215A produced a decreased, rather than enhanced protein C activity.*** The Examiner then alleged that "the skilled artisan would know that each mutation produces a thrombin variant having enhanced anti-coagulation activity, [or enhanced ratio of protein C activity to fibrinogen clotting activity]." *See* Final Office Action, page 10.

Applicants respectfully submit that ***if the motivation to combine the two references were really that obvious as the Examiner alleged, the Examiner would have asserted the motivation based on the skilled artisan's desire to provide an enhanced PC/PF ratio at the first place, rather than alleged "the skilled artisan's desire to provide a thrombin variant with enhanced protein C activation."*** The Examiner would not have to scramble to calculate the PC/PF ratio in each cited reference after Applicants had brought the experimental results of the invention to the Examiner's attention in the prior June 20, 2006 response to the First Office Action.

Accordingly, even if "the skilled artisan had the ***desire to provide a thrombin variant with enhanced protein C activity and decreased fibrinogen cleavage,***" as alleged by the Examiner, the skilled artisan at the time the invention was made would not have understood that

Arosio teaches, suggests, or provides a motivation to combine the W215A with the E217A to arrive at the claimed invention.

(Reply B): ***Arosio's statement that "further studies are necessary to identify more precisely the epitopes for protein C binding" cannot be a teaching or suggestion or providing a motivation*** to do this by introducing W215A into the primary reference's E217 ***because Arosio concluded that "the environment of W215 of thrombin is not significantly involved in the binding of protein C."*** Thus, ***skilled artisan in the field at the time the invention was made would not have understood Arosio's teaching as a suggestion to introduce W215A into E217A*** in order to identify more precisely the epitopes for protein C binding.

Further, Arosio's statement that "[f]uture studies are necessary to identify more precisely the epitopes for protein C and PAR-1 binding, and that [t]he penultimate ß-strand of the B chain hosts highly conserved residues such as W215 and G216 whose mutation affects both the specificity and catalytic activity of the enzyme, and that this region represents an important target for future mutagenesis studies" ***is not the same as teaching, suggesting or providing a motivation to further substitute E217 on the top of W215A,*** which is required by the present invention.

Also, Arosio's statement that "[t]he differential effect on binding of fibrinogen and protein C makes the W215A mutant the best anti-coagulant thrombin reported to date" ***is not the same as suggesting or teaching to further combine W215A with E217A.***

Furthermore, Arosio's statement that "the gain in anti-coagulant potency is larger [for the W215A mutant] than that of the E217 A mutant" ***is not the same as suggesting, teaching, or motivating to do W215A/E217A*** as the Applicants have done.

Moreover, obviousness cannot be based on mere speculation or conjecture. Arosio et al.'s ***explanation*** for the effects seen in the W215A mutants "that perturbation of residue 215 propagates to the neighbor residues G216 and E217, producing changes in the access to the S1 site and reduce Na+ binding" ***is not the same as teaching or suggesting or providing a motivation to the skilled artisan to further introducing the W215A into the E217 in order to make a double mutant E217/W215A.***

(Reply C): Applicants respectfully submit that the Examiner not only erred in making impermissible hindsight vision, but also erred in over-simplifying the complexity of cooperative changes in Enzymatic conformation here.

The life science/Biotechnology being in the area of unpredictable art, a synergistic effect cannot reasonably or necessarily be expected from allosteric sites. According to Metzler, cooperative phenomenon is more complex than many models having been proposed. *E.g. see* page 349, left column, second paragraph; and page 476, right column, last paragraph.

Allosteric interactions do not necessarily lead to synergy. Metzler does not teach that the allosteric sites of enzymes act synergistically in both the activation and inhibition of the enzyme. On the contrary, Metzler teaches that ***allosteric interactions "lead to cooperativity or anticooperativity in binding."*** (Emphasis added.). *See* Metzler, page 476, right column, third paragraph.

Even if given the benefit of the doubt that the allosteric interactions were ***only cooperative*** in Enzyme activity, ***the cooperativity is by no means synergy***. Metzler teaches that cooperative binding of substrates to enzymes is analogous to that of cooperative binding of oxygen by hemoglobin. McLennan reported that Hemoglobin has three ***allosteric sites***, and their ***interactions are non-synergistic but are simply additive***. *See* attached Abstract (*Biochemistry and Molecular Biology International*, Vol. 44, No. 1, pages 175-183, 1998). Rao G.S. reported that Ascaris suumphosphofructokinase has two ***allosteric sites***, one for fructose 2,6-biphosphate and one for AMP, and that their effects on the enzyme ***are additive and not synergistic***. *See* attached Abstract (*Archives of Biochemistry and Biophysics*, Vol. 365, No. 2, pages 335-343(9), 1999.)

The foregoing examples sufficiently demonstrate that the life science is unpredictable art and that results from experimental manipulations at the molecular or genetic level are not always obvious or predictable for skilled artisan in the field. Thus, the Examiner's assertions that allosteric sites act synergistically were not scientifically correct.

(Reply D): Having acknowledged (again, after the Applicants had pointed it out in the prior response mentioned above) that each of single mutant W215A (Arosio et al.; Table 1) and E217A (Gibbs et al; Table 1) had a decreased Protein C activity, the Examiner then alleged that "the skilled artisan would know that it is the ratio of protein C activity to fibrinogen clotting

activity (PC/PF), not the absolute protein C activity, that determines whether the action of thrombin will be primarily anti-coagulation, via the activation of protein C, or procoagulation, via cleavage of thrombin (Arosio et al, pg 8095, parg1)."

Applicants respectfully submit that ***Arosio does not teach*** that "it is the ***ratio*** of protein C activity to fibrinogen clotting activity (PC/PF), not the absolute protein C activity, that determines whether the action of thrombin will be primarily anti-coagulation, via the activation of protein C, or procoagulation, via cleavage of thrombin." ***It is Applicants who teach the ratio of PA/FC in the specification.*** *See* the specification, page 16. Applicants respectfully submit that the Examiner was committing an error in making impermissible hindsight here.

Furthermore, ***the art does not teach it is the ratio PC/PF that determines*** whether the action of thrombin will be primarily anti-coagulation, via the activation of protein C, or procoagulation." ***The art teaches*** that Thrombin is an allosteric enzyme existing in two forms, slow and fast. The two forms are significantly populated in vivo, and the ***allosteric equilibrium*** can be affected by the binding of effectors and natural substrates. The fast form is procoagulant because it cleaves fibrinogen with higher specificity; the slow form is anticoagulant because it cleaves protein C with higher specificity. *See* Attached Dang et al. (Abstract, PNAS, Vol. 92, 5977-5981, 1955.)

Thus, ***it is the allosteric equilibrium, or the ratio of specificity to cleave Protein C (i.e., slow form) to specificity to cleave fibrinogen (i.e., fast form), that decides whether the net effect of thrombin in vivo is aniticoagulation or procoagulation.***

Even if the Examiner's allegation "the skilled artisan would know that it is the ratio of protein C activity to fibrinogen clotting activity (PC/PF), not the absolute protein C activity, that determines whether the action of thrombin will be primarily anti-coagulation" were scientifically sound, the skilled artisan still would not know to combine references to arrive at the claimed invention because the cited reference do not provide the motivation to do so.

Accordingly, the claimed invention is non-obvious over the Gibbs in view of Arosio. The unexpected synergistic results found by the Applicants should not be treated lightly and dismissed causally by the Examiner. Neither the primary reference nor the secondary reference provides the motivation to combine the references to do what the invention has done. Thus, Applicants respectfully request that the obviousness rejection be withdrawn.

New Claims 59-60

New claims 59-60 are also nonobvious over the combination of cited references at least for depending from a nonobvious claim, claim 1. Moreover, new claims 59-60 require ***the PA/FC ratio greater than 200 and 1000,*** respectively. Neither the primary reference nor the secondary reference teaches the ratio PA/FC, let alone the ratio PA/FC greater than 200 and/or 1000. Therefore, new claims 59-60 are nonobvious over the combination of Gibbs and Arosio.

CONCLUSION

Applicants respectfully submit that the foregoing Amendment and Response place this application in condition for allowance. If the Examiner believes that there are any issues that can be resolved by a telephone conference, or that there are any informalities that can be corrected by an Examiner's amendment, please call the undersigned at 404-495-3678.

Respectfully submitted,
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